

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:** Please amend the claims as follows:

**We claim:**

**Claim 1. (Previously Presented)** A pharmaceutical composition comprising at least one agent as compound I which modulates the biological function of one or several of the VEGF/VEGF receptor systems, and further comprising at least one agent as compound II which modulates the biological function of one or several of the Angiopoietin/Tie receptor systems.

**Claim 2. (Previously Presented)** A pharmaceutical composition comprising at least one agent as compound I which is targeted to the endothelium via one or several of the VEGF/VEGF receptor systems, and further comprising at least one agent as compound II which modulates the biological function of one or several of the Angiopoietin/Tie receptor systems.

**Claim 3. (Cancelled)**

**Claim 4. (Previously Presented)** A pharmaceutical composition comprising at least one agent as compound I which modulates the biological function of one or several of the VEGF/VEGF receptor systems, and further comprising at least one agent as compound II which is targeted to the endothelium via one or several of the Angiopoietin/Tie receptor systems.

**Claim 5. (Previously Presented)** A pharmaceutical composition comprising at least one agent as compound I which is targeted to the endothelium via one or several of the VEGF/VEGF receptor systems, and further comprising at least one agent as compound II which is targeted to the endothelium via one or several of the Angiopoietin/Tie receptor systems.

**Claim 6. (Previously Presented)** A pharmaceutical composition

comprising at least one agent as compound I which modulates the biological function of one or several of the VEGF/VEGF receptor systems, and further comprising at least one agent as compound II which is targeted to the endothelium via one or several of the VEGF/VEGF receptor systems.

**Claim 7. (Previously Presented)** A pharmaceutical composition comprising at least one agent as compound I which modulates the biological function of one or several of the Angiopoietin/Tie receptor systems, and further comprising at least one agent as compound II which is targeted to the endothelium via one or several of the Angiopoietin/Tie receptor systems.

**Claim 8. (Withdrawn)** Pharmaceutical compositions comprising one or several agents which interfere with both the function of one or several of the VEGF/VEGF receptor systems and the function of one or several of the Angiopoietin/Tie receptor systems.

**Claim 9. (Previously Presented)** A pharmaceutical composition according to claim 1 which is adopted for simultaneous or separate sequential therapeutic application.

**Claim 10. (Previously Presented)** A pharmaceutical composition according to claim 1 which comprises as compound I at least one of

- a) a compound which inhibits receptor tyrosine kinase activity,
- b) a compound which inhibits ligand binding to receptors,
- c) a compound which inhibits activation of intracellular signal pathways of the receptors,
- d) a compound which inhibits or activates expression of a ligand or of a receptor of the VEGF or Tie receptor system,
- e) a delivery system comprising an antibody, a ligand, a high-affinity binding oligonucleotide or oligopeptide, or a liposome, which targets cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,
- f) a delivery system comprising an antibody, a ligand, a high-affinity binding

oligonucleotide or oligopeptide, or a liposome, which is targeted to the endothelium and induce necrosis or apoptosis.

**Claim 11. (Previously Presented)** A pharmaceutical composition according to claim 1 which comprises as compound II at least one of

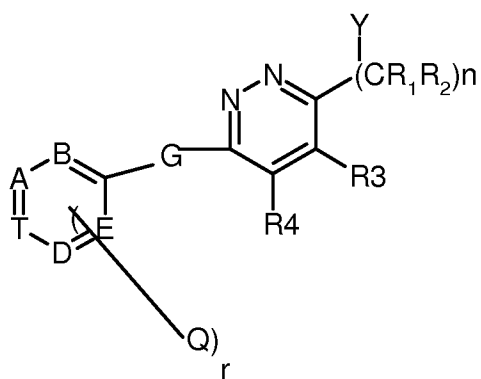
- f) a compound which inhibits receptor tyrosine kinase activity,
- g) a compound which inhibits ligand binding to receptors,
- h) a compound which inhibits activation of intracellular signal pathways of the receptors,
- i) a compound which inhibits or activates expression of a ligand or of a receptor of the VEGF or Tie receptor system,
- j) a delivery system comprising an antibody, a ligand, a high-affinity binding oligonucleotide or oligopeptide, or a liposome, which targets cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,
- k) a delivery system comprising an antibody, a ligand, a high-affinity binding oligonucleotide or oligopeptide, or a liposome, which is targeted to the endothelium and induce necrosis or apoptosis.

**Claim 12. (Withdrawn)** Pharmaceutical compositions according to claim 1 which comprise as compound I and/or II at least one of Seq. ID Nos. 1-59.

**Claim 13. (Withdrawn)** Pharmaceutical compositions according to claim 1 which comprise as compound I and/or II SEQ ID NO:60.

**Claim 14. (Withdrawn, Currently Amended)** ~~Pharmaceutical compositions~~ A pharmaceutical composition according to claim 1 which comprise as compound I and/or II at least one of sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTFconjugate.

**Claim 15. (Withdrawn, Currently Amended)** ~~Pharmaceutical compositions~~ A pharmaceutical composition according to claim 1 which comprise as compound I and/ or II at least one small molecule of ~~general~~ general formula I



I,

in which

r has the meaning of 0 to 2,

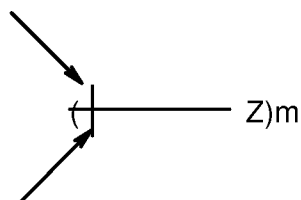
n has the meaning of 0 to 2;

R<sub>3</sub> und R<sub>4</sub>

a) each independently from each other have the meaning of lower alkyl,

b) together form a bridge of general partial formula

II,



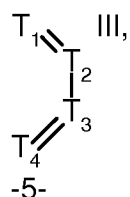
II,

wherein the binding is via the two terminal C- atoms,

and

m has the meaning of 0 to 4; or

c) together form a bridge of partial formula III



wherein one or two of the ring members  $T_1, T_2, T_3, T_4$  has the meaning of nitrogen, and each others have the meaning of CH, and the binding is via the atoms  $T_1$  and  $T_4$ ;

G has the meaning of  $C_1 - C_6$  - alkyl,  $C_2 - C_6$  - alkylene or  $C_2 - C_6$  - alkenylene; or  $C_2 - C_6$  - alkylene or  $C_3 - C_6$  - alkenylene, which are substituted with acyloxy or hydroxy;  $-CH_2-O-$ ,  $-CH_2-S-$ ,  $-CH_2-NH-$ ,  $-CH_2-O-CH_2-$ ,  $-CH_2-S-CH_2-$ ,  $-CH_2-NH-CH_2$ , oxa ( $-O-$ ), thia ( $-S-$ ) or imino ( $-NH-$ ),

A, B, D, E and T independently from each other have the meaning of N or CH, with the proviso that not more than three of these Substituents have the meaning of N,

Q has the meaning of lower alkyl, lower alkyloxy or halogene,  
 $R_1$  and  $R_2$  independently from each other have the meaning of H or lower alkyl,

X has the meaning of imino, oxa or thia;

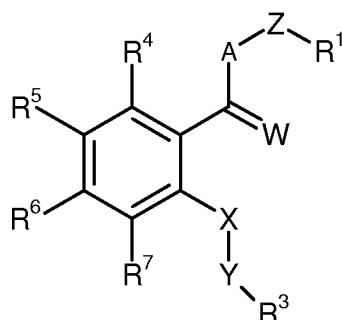
Y has the meaning of hydrogen, unsubstituted or substituted aryl, heteroaryl, or unsubstituted or substituted cycloalkyl; and

Z has the meaning of amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherificated or esterificated hydroxy, nitro, cyano, carboxy, esterificated carboxy, alkanoyl, carbamoyl, N-mono- or N, N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower-alkyl-thio, alkyl-phenyl-thio, phenylsulfinyl, phenyl-lower-alkyl-sulfinyl, alkylphenylsulfinyl, phenylsulfonyl, phenyl-lower-alkan-sulfonyl, or alkylphenylsulfonyl,

whereas, if more than one rest Z is present ( $m > 2$ ), the substituents Z are equal or different from each other,

and

wherein the bonds marked with an arrow are single or double bonds; or an N-oxide of said compound, wherein one or more N-atoms carry an oxygen atom, or a salt thereof, and/or a compound of general formula IV



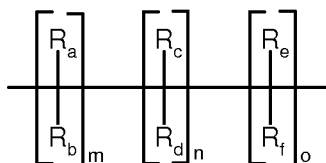
IV

in which

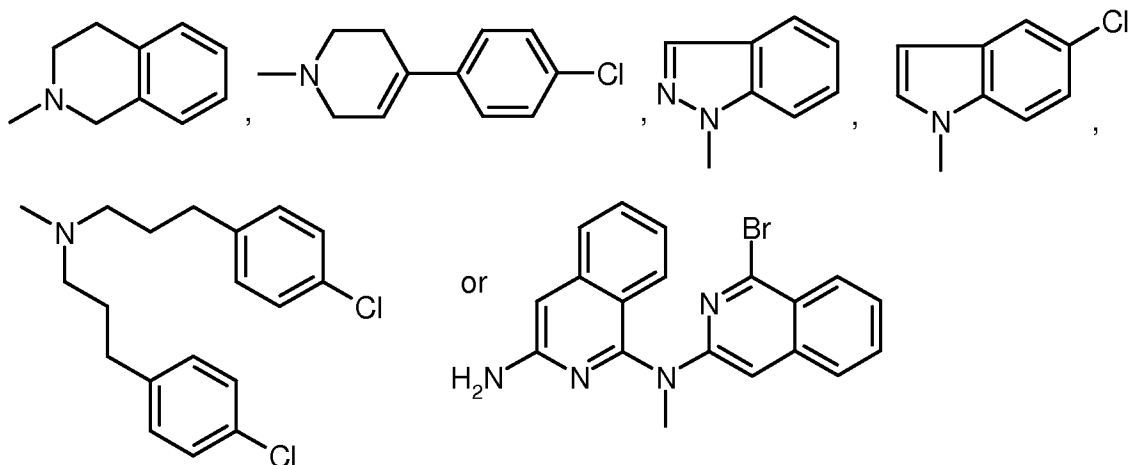
A has the meaning of group  $=NR^2$ ,

W has the meaning of oxygen, sulfur, two hydrogen atoms or the group  $=NR^8$ ,

Z has the meaning of the group  $=NR^{10}$  or  $=N-$ ,  $-N(R^{10})-(CH_2)_q-$ , branched or unbranched  $C_{1-6}$ -Alkyl or is the group



or A, Z and  $R^1$  together form the group



m, n and o

has the meaning of 0 – 3,

q

has the meaning of 1 – 6,

R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub>, R<sub>d</sub>, R<sub>e</sub>, R<sub>f</sub>

independently from each other have the meaning of hydrogen, C<sub>1-4</sub> alkyl or the group =NR<sup>10</sup>, and/ or R<sub>a</sub> and/ or R<sub>b</sub> together with R<sub>c</sub> and or R<sub>d</sub> or R<sub>c</sub> together with R<sub>e</sub> and/ or R<sub>f</sub> form a bound, or up to two of the groups R<sub>a</sub>-R<sub>f</sub> form a bridge with each up to 3 C-atoms with R<sup>1</sup> or R<sup>2</sup>,

X

has the meaning of group =NR<sup>9</sup> or =N-,

Y

has the meaning of group -(CH<sub>2</sub>)<sub>p</sub>,

p

has the meaning of integer 1-4,

R<sup>1</sup>

has the meaning of unsubstituted or optionally substituted with one or more of halogene, C<sub>1-6</sub>-alkyl, or C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-alkoxy, which is optionally substituted by one or more of halogen, or is unsubstituted or substituted aryl or heteroaryl,

R<sup>2</sup>

has the meaning of hydrogen or C<sub>1-6</sub>-alkyl, or form a bridge with up to 3 ring atoms with R<sub>a</sub>-R<sub>f</sub> together with Z or R<sub>1</sub>,

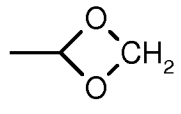
R<sup>3</sup>

has the meaning of monocyclic or bicyclic aryl or heteroaryl which is unsubstituted or optionally substituted with one or more of für halogen, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy or hydroxy,

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup>

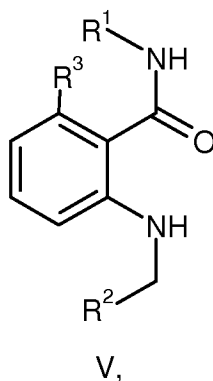
independently from each other have the meaning of

hydrogen, halogene or C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-carboxyalkyl, which are unsubstituted or optionally substituted with one or more of halogene, or R<sup>5</sup> and R<sup>6</sup> together form the group



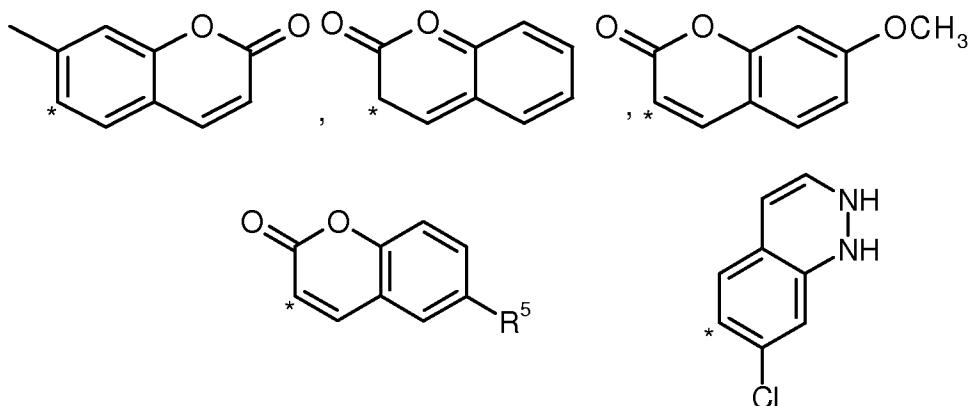
R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> independently from each other have the meaning of hydrogen or C<sub>1-6</sub>-alkyl, as well as their isomers and salts,

and/ or a compound of general formula V



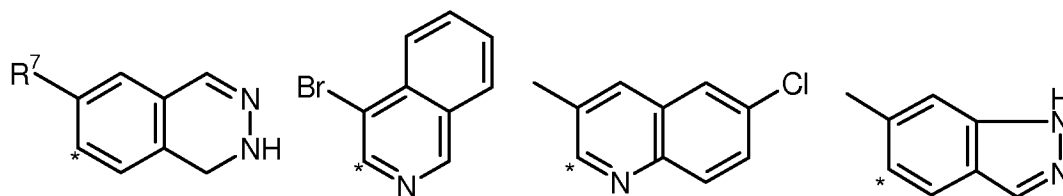
in which

R<sup>1</sup> has the meaning of group

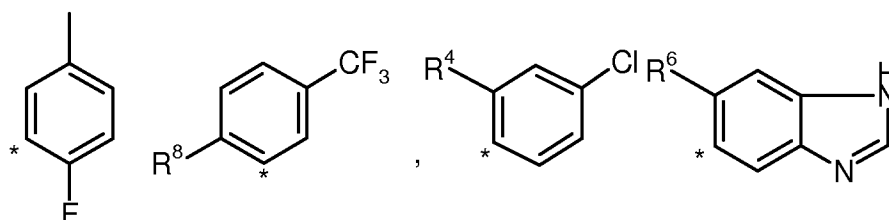




in which R<sup>5</sup> is chloro, bromo or the group -OCH<sub>3</sub>,



in which R<sup>7</sup> is -CH<sub>3</sub> or chloro,

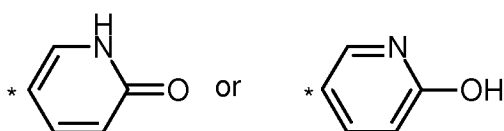


in which R<sup>8</sup> is -CH<sub>3</sub>, fluoro, chloro, or -CF<sub>3</sub>,

in which R<sup>4</sup> is fluoro, chloro, bromo, -CF<sub>3</sub>, -N=C, -CH<sub>3</sub>, -OCF<sub>3</sub> or -CH<sub>2</sub>OH

in which R<sup>6</sup> is -CH<sub>3</sub> or chloro

R<sup>2</sup> has the meaning of pyridyl or the group



and

R<sup>3</sup> has the meaning of hydrogen or fluoro,

as well as their isomers and salts.

**Claim 16. (Withdrawn, Currently Amended)** ~~Pharmaceutical compositions~~ A pharmaceutical composition according to claim 15 which comprise as compound I and/or II (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate.

**Claim 17. (Withdrawn, Currently Amended)** ~~Pharmaceutical—compositions~~ A pharmaceutical composition according to claim 1 which comprise as compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, and as compound II (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, with the provision that compound I is not identically to compound II.

**Claim 18. (Withdrawn, Currently Amended)** ~~Pharmaceutical—compositions~~ A pharmaceutical composition according to claim 1 which comprise as compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate and as compound II sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate.

**Claim 19. (Withdrawn, Currently Amended)** ~~Pharmaceutical—compositions~~ A pharmaceutical composition according to claim 1 which comprise as compound I mAB 4301-42-35 and as compound II sTie2, and/ or scFv-tTF conjugate.

**Claim 20. (Withdrawn, Currently Amended)** ~~Pharmaceutical—compositions~~ A pharmaceutical composition according to claim 1 which comprise as compound I scFv-tTF conjugate and as compound II sTie2 and/ or mAB 4301-42-35.

**Claim 21. (Withdrawn, Currently Amended)** ~~Pharmaceutical—compositions~~ A pharmaceutical composition according to claim 1 which comprise as compound I L19 scFv-tTF conjugate and as compound II sTie2.

**Claim 22. (Withdrawn, Currently Amended)** ~~Use of pharmaceutical compositions according to claim 1, for the production of a medicament for the treatment of~~ A method of treating tumors, cancers, psoriasis, arthritis, ~~such as~~ rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, ~~such as~~ diabetic retinopathy, neovascular glaucoma, kidney diseases, ~~such as~~ glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplantation rejections, and glomerulopathy, fibrotic diseases, ~~such as~~ cirrhotic liver, mesangial cell

proliferative diseases, ~~arteriosclerosis~~ arteriosclerosis, damage of nerve tissues, or for the suppression of the ascites formation in patients and or for the suppression of VEGF oedemas in a subject, comprising administering into said subject an effective amount of the pharmaceutical composition of claim 1.

**Claim 23. (New)** A method of treating a tumor or tumor metastasis in a subject, comprising administering into said subject an effective amount of the pharmaceutical composition of claim 1.

**Claim 24. (New)** The pharmaceutical composition of claim 1 wherein compound I is 4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate and compound II is sTie2.